



freepatentsonline

BAY-19-8004

Patent Number

Site Contents

Bookmark This Site

**Search Patents**

Use our search engine to find what you need

**Data and Analytical Services**

Complete custom solutions

**Syntax Reference**

Learn our powerful search syntax

**F.A.Q.**

About this site and our patent search engine

**Title:**

**Pde4 and pde3/4 inhibitors for use in t cachexia**

**Document Type and Number:**

United States Application 20060079540

**Link to this Page:**

<http://www.freepatentsonline.com/20060079540.html>

**Abstract:**

The invention relates to the use of a PDE4 or PDE3/4 inhibitor for

[Ads by Goooooogle](#)

[CA 19-9 Tumor Markers](#)

Interactive Presentation Learn about Cancer & Tumor Markers  
[www.fdi.com](http://www.fdi.com)

[Angiogenesis & Lucentis ®](#)

Find out how Lucentis ® may inhibit Angiogenesis. Visit the website.  
[www.Lucentis.com](http://www.Lucentis.com)

[Tempe Patent Attorney](#)

Technology, Software, Bus. Methods Boutique Quality & Low Fixed Fees  
[www.patentdoc.com](http://www.patentdoc.com)

[Grand Bay Dsl](#)

DSL Internet Service Provider CenturyTel Think Fast-\$19.95/month  
[www.CenturyTel.com](http://www.CenturyTel.com)

[Ads by Goooooogle](#)

[CA 19-9 Tumor Markers](#)

Interactive Presentation Learn about Cancer & Tumor Markers  
[www.fdi.com](http://www.fdi.com)

[Angiogenesis & Lucentis ®](#)

Find out how Lucentis ® may inhibit Angiogenesis. Visit the website.  
[www.Lucentis.com](http://www.Lucentis.com)

[Tempe Patent Attorney](#)

Technology, Software, Bus. Methods Boutique Quality & Low Fixed Fees  
[www.patentdoc.com](http://www.patentdoc.com)

[Grand Bay Dsl](#)

DSL Internet Service Provider CenturyTel Think Fast-\$19.95/month  
[www.CenturyTel.com](http://www.CenturyTel.com)

**Inventors:** Schmidt, Mathias;  
**Application Number:** 535815  
**Filing Date:** 2003-11-26  
**Publication Date:** 2006-04-13  
**View Patent Images:** [Login or Create Account \(Free!\)](#)  
**Related Patents:** [View patents that cite this patent](#)  
**Export Citation:** [Click for automatic bibliography generation](#)  
**Assignee:** Altana Pharma AG  
**Primary Class:** 514/263.34  
**Other Classes:**  
**International Classes:** A61K 31/522 20060101 A61K031/522; A61K 31/513 20060101 A61K031/473; A61K 31/426 20060101 A61K031/426; A61K 31/2  
**Foreign Patent References:**

Date	Code	Application Number
Nov 27, 2002	EP	02026548.4

**Attorney, Agent or Firm:** NATH & ASSOCIATES PLLC 112 South West Street Alexandria VA  
**Claims:**

1. A method for treating cachexia, comprising administering to a patient in need of a PDE4 inhibitor or a pharmaceutically acceptable derivative thereof, a pharmaceutically acceptable derivative thereof.
2. The method according to claim 1, whereby the cachexia is a result of cancer, A infections, burns, chronic cardiac insufficiency, cirrhosis of the liver, COPD or chr
3. The method according to claim 2, wherein the cachexia is a result of cancer.
4. The method according to claim 3, wherein the cancer is selected from the group cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, l cancer, thyroid cancer, pancreatic cancer, prostate cancer and bladder cancer.
5. The method as claimed in claim 1, wherein the PDE4 inhibitor or PDE3/4 inhibi

consisting of CDC-998, SH-636, D-4396, SCH-351591, IC-485, CC-1088, KW-449, methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine [Research-Code: V-1129], 3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzo-- diazepin-3(R)-yl]pyridine-4-carboxamide [Research-Code: ORG-202], 1-propyl-1H-purine-2,6-dione [INN: AROFYLLINE], 3-[3-(Cyclopentyloxy)-4-methoxymethyl]-1H-indol-3-yl]-2-oxoacetamide [Research-Code: AWD-12-281], N-(3,5-dichloro-4-fluorobenzyl)-1H-indol-3-yl]-2-oxoacetamide [Research-Code: AWD-12-343], 8-xanthine [INN: CIPAMFYLLINE], Tetrahydro-5-[4-methoxy-3-[(1S,2S,4R)-2-norbornyl]-1,3-dihydro-1H-benzofuran-2-yl]-1,3-dihydro-1H-benzofuran-2-one [Research-Code: CDC-801], Methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl)-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-1,3-dioxane-1-carboxylic acid [Research-Code: BAY-19-8004], (Z)-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-1,3-dioxane-1-carboxylic acid [Research-Code: DARBUFELONE], cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl]methoxy-N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide and pharmaceutically acceptable derivatives thereof.

6. The method as claimed in claim 1, wherein the PDE4 inhibitor or PDE3/4 inhibitor consisting of (-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydro-6H-benzo-[c][1,6]naphthyridine [INN: PUMAFENTRINE], 3-Cyclo-propylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], and pharmaceutically acceptable derivative thereof.

7. The method as claimed in claim 1, wherein the PDE3/4 inhibitor is (-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydro-6H-benzo-[c][1,6]naphthyridine [INN: PUMAFENTRINE], 3-Cyclo-propylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], and pharmaceutically acceptable derivative thereof.

8. The method as claimed in claim 1, wherein the PDE4 inhibitor is 3-Cyclopropyl-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable derivative thereof.

9. The method as claimed in claim 8, wherein the PDE4 inhibitor is 3-Cyclopropyl-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable derivative thereof.

10.-12. (canceled)

13. The method according to claim 1, wherein the PDE4 inhibitor or the PDE3/4 inhibitor or the pharmaceutically acceptable derivative thereof is used in the induction of a cachectic symptom.

14. A method for treating cachexia in a human afflicted with cancer comprising the steps of administering to a human in need thereof a therapeutically effective amount of a PDE4 inhibitor or a PDE3/4 inhibitor or a pharmaceutically acceptable derivative thereof.

15. The method according to claim 14, whereby the survival period of a cancer patient is prolonged.

16. A method for improving the response to chemo- and/or radiation-therapy in a human afflicted with cachexia comprising the steps of administering to a human in need thereof an effective amount of a PDE4 inhibitor or a pharmaceutically acceptable derivative thereof.

#### Description:

#### FIELD OF APPLICATION OF THE INVENTION

[0001] The present invention relates to PDE4 inhibitors and PDE3/4 inhibitors for substances used in accordance with this invention are known active compounds from the prior art.

#### PRIOR ART

[0002] WO9923076, WO0009504, WO0147914, WO0157036, WO02060898, U.S. Pat. No. 5,728,844, EP1229034 list therapeutically active compounds and their use for the treatment of numerous diseases.

#### DESCRIPTION OF THE INVENTION

[0003] Cachexia is a syndrome of wasting associated with many forms of cancer, cirrhosis, chronic kidney insufficiency, COPD (chronic obstructive pulmonary disease). The clinical picture of cachexia includes weight loss, anorexia (i.e. loss of appetite), muscle mass and loss of fat mass, muscle atrophy, gain in the proportion of body-water. Generally, cachexia associated with cancer is not a local effect of a tumor, but is a systemic metabolic effects, i.e. it is a type of paraneoplastic syndrome. Clinical trials directed at reversing the symptoms of cachexia have failed to reverse the symptoms of cachexia. The pattern of weight loss in cancer patients is different from normal starvation. The normal adaptive response to nutrient deprivation is to spare protein, resulting in loss of fat and relative preservation of lean body tissue. In cancer patients, experience severe and incapacitating muscle wasting with relative sparing of adipose tissue.

[0004] Undisputedly, there is a medical need for better treatment options of cachexia as a result of cancer. Cachexia is seen in more than 60% of cancer patients. Cachexia as a result of cancer therapy is very often dependent on the presence or absence of cachexia. A poorer response to chemo- and radiation therapy are observed in patients with severe cachexia. Am. J. Med 69: 491-497 (1980); Kern et al., J. Parenter. Enter. Nutr. 12: 286-29 (1987). Cachexia is one of the most important contributors that lead to loss of quality of life in cancer patients and to increased mortality.

[0005] In general, two different approaches have been undertaken to manage cachexia. Firstly, nutritional supplementation with improved diet or, secondly, drugs to increase appetite. But--like megestrol acetate--drugs to increase appetite have generally been ineffective, megestrol acetate only being capable of restoring adipose body weight.

[0006] Although little is known about the precise mechanisms of cachexia, recent data suggest that production and release of cytokines such as TNF- $\alpha$ , Interleukin-1, Interleukin-6 are involved in the induction of cachexia. Knapp et al. (1991) observed elevated TNF levels in advanced stage IV breast cancer patients [Knapp et al., Ann Clin. Biochem., 28: 1-6 (1991)]. It is reported that antibodies to TNF could significantly reduce the loss of carcass protein in a rat model [Sherry et al., FASEB J. 3: 1956-1962 (1989)]. Fong et al. found that IL-1 and LPS as inducers of anorexia and cachexia in rats [Fong et al., Am. J. Physiol. 256: R100-R106 (1988)]. It is reviewed that further cytokines, e.g. Leukemia Inhibitory Factor (LIF), Ciliary Neurotrophic Factor (CNTF), Interferon- $\gamma$ , are associated with cachexia [Mattys and Billiau, Nutrition 1: 1-6 (1995)].

[0007] These data indicate that multiple cytokines secreted from tumor and host cells are able to cause the metabolic changes associated with cachexia and finally to induce cachexia.

[0008] It is the object of the present invention to make available a treatment of cachexia under the following conditions: (1) Suppression or neutralization of cytokines involved in induction of cachexia, (2) influencing the bioactivity of several and not only of a single cytokine.

[0009] Surprisingly, it has now been found that the use of a PDE4 or a PDE3/4 inhibitor in the treatment of cachexia is effective under the following conditions.

[0010] In a first embodiment of this invention, there is provided the use of a PDE4 inhibitor pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the treatment of cachexia.

[0011] According to this invention, "PDE4 inhibitor" refers to a selective phosphodiesterase inhibitor which preferentially inhibits the type 4 phosphodiesterase (PDE4) when compared to other phosphodiesterases, e.g. type 1, 2, 3, 5, etc. (PDE1, PDE2, PDE3, PDE5, etc.). According to this invention, a compound preferentially inhibiting PDE4 refers to a compound having a lower IC<sub>50</sub> for PDE4 inhibition is about 10 times lower than the IC<sub>50</sub> for inhibition of other known phosphodiesterases, e.g. 1, 2, 3, 5, etc.) and therefore is more potent to inhibit PDE4. Analogously, the term "PDE3/4 inhibitor" refers to a compound having a lower IC<sub>50</sub> for the type 3/4 phosphodiesterases and therefore to inhibit PDE3/4.

[0012] Methods to determine the activity and selectivity of a phosphodiesterase inhibitor are well known in the art. In this connection it may be mentioned, for example, the method of G. L. S. (Br J Pharmacol 10: 69-92, 1979), Giembycz et al. (Br J Pharmacol 118:1945-1958) and the scintillation proximity assay of Amersham Pharmacia Biotech.

[0013] Possible PDE4 or PDE3/4 inhibitors within the meaning of the present invention are cited expressis verbis as an example, or described or claimed in the following applications and patents: DE 1545687, DE 2028869, DE 2123328, DE 2315801, DE 2315802, DE 2315803, DE 2315804, DE 2315805, DE 2315806, DE 2315807, DE 2315808, DE 2315809, DE 2315810, DE 2315811, DE 2315812, DE 2315813, DE 2315814, DE 2315815, DE 2315816, DE 2315817, DE 2315818, DE 2315819, DE 2315820, DE 2315821, DE 2315822, DE 2315823, DE 2315824, DE 2315825, DE 2315826, DE 2315827, DE 2315828, DE 2315829, DE 2315830, DE 2315831, DE 2315832, DE 2315833, DE 2315834, DE 2315835, DE 2315836, DE 2315837, DE 2315838, DE 2315839, DE 2315840, DE 2315841, DE 2315842, DE 2315843, DE 2315844, DE 2315845, DE 2315846, DE 2315847, DE 2315848, DE 2315849, DE 2315850, DE 2315851, DE 2315852, DE 2315853, DE 2315854, DE 2315855, DE 2315856, DE 2315857, DE 2315858, DE 2315859, DE 2315860, DE 2315861, DE 2315862, DE 2315863, DE 2315864, DE 2315865, DE 2315866, DE 2315867, DE 2315868, DE 2315869, DE 2315870, DE 2315871, DE 2315872, DE 2315873, DE 2315874, DE 2315875, DE 2315876, DE 2315877, DE 2315878, DE 2315879, DE 2315880, DE 2315881, DE 2315882, DE 2315883, DE 2315884, DE 2315885, DE 2315886, DE 2315887, DE 2315888, DE 2315889, DE 2315890, DE 2315891, DE 2315892, DE 2315893, DE 2315894, DE 2315895, DE 2315896, DE 2315897, DE 2315898, DE 2315899, DE 2315900, DE 2315901, DE 2315902, DE 2315903, DE 2315904, DE 2315905, DE 2315906, DE 2315907, DE 2315908, DE 2315909, DE 2315910, DE 2315911, DE 2315912, DE 2315913, DE 2315914, DE 2315915, DE 2315916, DE 2315917, DE 2315918, DE 2315919, DE 2315920, DE 2315921, DE 2315922, DE 2315923, DE 2315924, DE 2315925, DE 2315926, DE 2315927, DE 2315928, DE 2315929, DE 2315930, DE 2315931, DE 2315932, DE 2315933, DE 2315934, DE 2315935, DE 2315936, DE 2315937, DE 2315938, DE 2315939, DE 2315940, DE 2315941, DE 2315942, DE 2315943, DE 2315944, DE 2315945, DE 2315946, DE 2315947, DE 2315948, DE 2315949, DE 2315950, DE 2315951, DE 2315952, DE 2315953, DE 2315954, DE 2315955, DE 2315956, DE 2315957, DE 2315958, DE 2315959, DE 2315960, DE 2315961, DE 2315962, DE 2315963, DE 2315964, DE 2315965, DE 2315966, DE 2315967, DE 2315968, DE 2315969, DE 2315970, DE 2315971, DE 2315972, DE 2315973, DE 2315974, DE 2315975, DE 2315976, DE 2315977, DE 2315978, DE 2315979, DE 2315980, DE 2315981, DE 2315982, DE 2315983, DE 2315984, DE 2315985, DE 2315986, DE 2315987, DE 2315988, DE 2315989, DE 2315990, DE 2315991, DE 2315992, DE 2315993, DE 2315994, DE 2315995, DE 2315996, DE 2315997, DE 2315998, DE 2315999, DE 2316000, DE 2316001, DE 2316002, DE 2316003, DE 2316004, DE 2316005, DE 2316006, DE 2316007, DE 2316008, DE 2316009, DE 2316010, DE 2316011, DE 2316012, DE 2316013, DE 2316014, DE 2316015, DE 2316016, DE 2316017, DE 2316018, DE 2316019, DE 2316020, DE 2316021, DE 2316022, DE 2316023, DE 2316024, DE 2316025, DE 2316026, DE 2316027, DE 2316028, DE 2316029, DE 2316030, DE 2316031, DE 2316032, DE 2316033, DE 2316034, DE 2316035, DE 2316036, DE 2316037, DE 2316038, DE 2316039, DE 2316040, DE 2316041, DE 2316042, DE 2316043, DE 2316044, DE 2316045, DE 2316046, DE 2316047, DE 2316048, DE 2316049, DE 2316050, DE 2316051, DE 2316052, DE 2316053, DE 2316054, DE 2316055, DE 2316056, DE 2316057, DE 2316058, DE 2316059, DE 2316060, DE 2316061, DE 2316062, DE 2316063, DE 2316064, DE 2316065, DE 2316066, DE 2316067, DE 2316068, DE 2316069, DE 2316070, DE 2316071, DE 2316072, DE 2316073, DE 2316074, DE 2316075, DE 2316076, DE 2316077, DE 2316078, DE 2316079, DE 2316080, DE 2316081, DE 2316082, DE 2316083, DE 2316084, DE 2316085, DE 2316086, DE 2316087, DE 2316088, DE 2316089, DE 2316090, DE 2316091, DE 2316092, DE 2316093, DE 2316094, DE 2316095, DE 2316096, DE 2316097, DE 2316098, DE 2316099, DE 2316100, DE 2316101, DE 2316102, DE 2316103, DE 2316104, DE 2316105, DE 2316106, DE 2316107, DE 2316108, DE 2316109, DE 2316110, DE 2316111, DE 2316112, DE 2316113, DE 2316114, DE 2316115, DE 2316116, DE 2316117, DE 2316118, DE 2316119, DE 2316120, DE 2316121, DE 2316122, DE 2316123, DE 2316124, DE 2316125, DE 2316126, DE 2316127, DE 2316128, DE 2316129, DE 2316130, DE 2316131, DE 2316132, DE 2316133, DE 2316134, DE 2316135, DE 2316136, DE 2316137, DE 2316138, DE 2316139, DE 2316140, DE 2316141, DE 2316142, DE 2316143, DE 2316144, DE 2316145, DE 2316146, DE 2316147, DE 2316148, DE 2316149, DE 2316150, DE 2316151, DE 2316152, DE 2316153, DE 2316154, DE 2316155, DE 2316156, DE 2316157, DE 2316158, DE 2316159, DE 2316160, DE 2316161, DE 2316162, DE 2316163, DE 2316164, DE 2316165, DE 2316166, DE 2316167, DE 2316168, DE 2316169, DE 2316170, DE 2316171, DE 2316172, DE 2316173, DE 2316174, DE 2316175, DE 2316176, DE 2316177, DE 2316178, DE 2316179, DE 2316180, DE 2316181, DE 2316182, DE 2316183, DE 2316184, DE 2316185, DE 2316186, DE 2316187, DE 2316188, DE 2316189, DE 2316190, DE 2316191, DE 2316192, DE 2316193, DE 2316194, DE 2316195, DE 2316196, DE 2316197, DE 2316198, DE 2316199, DE 2316200, DE 2316201, DE 2316202, DE 2316203, DE 2316204, DE 2316205, DE 2316206, DE 2316207, DE 2316208, DE 2316209, DE 2316210, DE 2316211, DE 2316212, DE 2316213, DE 2316214, DE 2316215, DE 2316216, DE 2316217, DE 2316218, DE 2316219, DE 2316220, DE 2316221, DE 2316222, DE 2316223, DE 2316224, DE 2316225, DE 2316226, DE 2316227, DE 2316228, DE 2316229, DE 2316230, DE 2316231, DE 2316232, DE 2316233, DE 2316234, DE 2316235, DE 2316236, DE 2316237, DE 2316238, DE 2316239, DE 2316240, DE 2316241, DE 2316242, DE 2316243, DE 2316244, DE 2316245, DE 2316246, DE 2316247, DE 2316248, DE 2316249, DE 2316250, DE 2316251, DE 2316252, DE 2316253, DE 2316254, DE 2316255, DE 2316256, DE 2316257, DE 2316258, DE 2316259, DE 2316260, DE 2316261, DE 2316262, DE 2316263, DE 2316264, DE 2316265, DE 2316266, DE 2316267, DE 2316268, DE 2316269, DE 2316270, DE 2316271, DE 2316272, DE 2316273, DE 2316274, DE 2316275, DE 2316276, DE 2316277, DE 2316278, DE 2316279, DE 2316280, DE 2316281, DE 2316282, DE 2316283, DE 2316284, DE 2316285, DE 2316286, DE 2316287, DE 2316288, DE 2316289, DE 2316290, DE 2316291, DE 2316292, DE 2316293, DE 2316294, DE 2316295, DE 2316296, DE 2316297, DE 2316298, DE 2316299, DE 2316300, DE 2316301, DE 2316302, DE 2316303, DE 2316304, DE 2316305, DE 2316306, DE 2316307, DE 2316308, DE 2316309, DE 2316310, DE 2316311, DE 2316312, DE 2316313, DE 2316314, DE 2316315, DE 2316316, DE 2316317, DE 2316318, DE 2316319, DE 2316320, DE 2316321, DE 2316322, DE 2316323, DE 2316324, DE 2316325, DE 2316326, DE 2316327, DE 2316328, DE 2316329, DE 2316330, DE 2316331, DE 2316332, DE 2316333, DE 2316334, DE 2316335, DE 2316336, DE 2316337, DE 2316338, DE 2316339, DE 2316340, DE 2316341, DE 2316342, DE 2316343, DE 2316344, DE 2316345, DE 2316346, DE 2316347, DE 2316348, DE 2316349, DE 2316350, DE 2316351, DE 2316352, DE 2316353, DE 2316354, DE 2316355, DE 2316356, DE 2316357, DE 2316358, DE 2316359, DE 2316360, DE 2316361, DE 2316362, DE 2316363, DE 2316364, DE 2316365, DE 2316366, DE 2316367, DE 2316368, DE 2316369, DE 2316370, DE 2316371, DE 2316372, DE 2316373, DE 2316374, DE 2316375, DE 2316376, DE 2316377, DE 2316378, DE 2316379, DE 2316380, DE 2316381, DE 2316382, DE 2316383, DE 2316384, DE 2316385, DE 2316386, DE 2316387, DE 2316388, DE 2316389, DE 2316390, DE 2316391, DE 2316392, DE 2316393, DE 2316394, DE 2316395, DE 2316396, DE 2316397, DE 2316398, DE 2316399, DE 2316400, DE 2316401, DE 2316402, DE 2316403, DE 2316404, DE 2316405, DE 2316406, DE 2316407, DE 2316408, DE 2316409, DE 2316410, DE 2316411, DE 2316412, DE 2316413, DE 2316414, DE 2316415, DE 2316416, DE 2316417, DE 2316418, DE 2316419, DE 2316420, DE 2316421, DE 2316422, DE 2316423, DE 2316424, DE 2316425, DE 2316426, DE 2316427, DE 2316428, DE 2316429, DE 2316430, DE 2316431, DE 2316432, DE 2316433, DE 2316434, DE 2316435, DE 2316436, DE 2316437, DE 2316438, DE 2316439, DE 2316440, DE 2316441, DE 2316442, DE 2316443, DE 2316444, DE 2316445, DE 2316446, DE 2316447, DE 2316448, DE 2316449, DE 2316450, DE 2316451, DE 2316452, DE 2316453, DE 2316454, DE 2316455, DE 2316456, DE 2316457, DE 2316458, DE 2316459, DE 2316460, DE 2316461, DE 2316462, DE 2316463, DE 2316464, DE 2316465, DE 2316466, DE 2316467, DE 2316468, DE 2316469, DE 2316470, DE 2316471, DE 2316472, DE 2316473, DE 2316474, DE 2316475, DE 2316476, DE 2316477, DE 2316478, DE 2316479, DE 2316480, DE 2316481, DE 2316482, DE 2316483, DE 2316484, DE 2316485, DE 2316486, DE 2316487, DE 2316488, DE 2316489, DE 2316490, DE 2316491, DE 2316492, DE 2316493, DE 2316494, DE 2316495, DE 2316496, DE 2316497, DE 2316498, DE 2316499, DE 2316500, DE 2316501, DE 2316502, DE 2316503, DE 2316504, DE 2316505, DE 2316506, DE 2316507, DE 2316508, DE 2316509, DE 2316510, DE 2316511, DE 2316512, DE 2316513, DE 2316514, DE 2316515, DE 2316516, DE 2316517, DE 2316518, DE 2316519, DE 2316520, DE 2316521, DE 2316522, DE 2316523, DE 2316524, DE 2316525, DE 2316526, DE 2316527, DE 2316528, DE 2316529, DE 2316530, DE 2316531, DE 2316532, DE 2316533, DE 2316534, DE 2316535, DE 2316536, DE 2316537, DE 2316538, DE 2316539, DE 2316540, DE 2316541, DE 2316542, DE 2316543, DE 2316544, DE 2316545, DE 2316546, DE 2316547, DE 2316548, DE 2316549, DE 2316550, DE 2316551, DE 2316552, DE 2316553, DE 2316554, DE 2316555, DE 2316556, DE 2316557, DE 2316558, DE 2316559, DE 2316560, DE 2316561, DE 2316562, DE 2316563, DE 2316564, DE 2316565, DE 2316566, DE 2316567, DE 2316568, DE 2316569, DE 2316570, DE 2316571, DE 2316572, DE 2316573, DE 2316574, DE 2316575, DE 2316576, DE 2316577, DE 2316578, DE 2316579, DE 2316580, DE 2316581, DE 2316582, DE 2316583, DE 2316584, DE 2316585, DE 2316586, DE 2316587, DE 2316588, DE 2316589, DE 2316590, DE 2316591, DE 2316592, DE 2316593, DE 2316594, DE 2316595, DE 2316596, DE 2316597, DE 2316598, DE 2316599, DE 2316600, DE 2316601, DE 2316602, DE 2316603, DE 2316604, DE 2316605, DE 2316606, DE 2316607, DE 2316608, DE 2316609, DE 2316610, DE 2316611, DE 2316612, DE 2316613, DE 2316614, DE 2316615, DE 2316616, DE 2316617, DE 2316618, DE 2316619, DE 2316620, DE 2316621, DE 2316622, DE 2316623, DE 2316624, DE 2316625, DE 2316626, DE 2316627, DE 2316628, DE 2316629, DE 2316630, DE 2316631, DE 2316632, DE 2316633, DE 2316634, DE 2316635, DE 2316636, DE 2316637, DE 2316638, DE 2316639, DE 2316640, DE 2316641, DE 2316642, DE 2316643, DE 2316644, DE 2316645, DE 2316646, DE 2316647, DE 2316648, DE 2316649, DE 2316650, DE 2316651, DE 2316652, DE 2316653, DE 2316654, DE 2316655, DE 2316656, DE 2316657, DE 2316658, DE 2316659, DE 2316660, DE 2316661, DE 2316662, DE 2316663, DE 2316664, DE 2316665, DE 2316666, DE 2316667, DE 2316668, DE 2316669, DE 2316670, DE 2316671, DE 2316672, DE 2316673, DE 2316674, DE 2316675, DE 2316676, DE 2316677, DE 2316678, DE 2316679, DE 2316680, DE 2316681, DE 2316682, DE 2316683, DE 2316684, DE 2316685, DE 2316686, DE 2316687, DE 2316688, DE 2316689, DE 2316690, DE 2316691, DE 2316692, DE 2316693, DE 2316694, DE 2316695, DE 2316696, DE 2316697, DE 2316698, DE 2316699, DE 2316700, DE 2316701, DE 2316702, DE 2316703, DE 2316704, DE 2316705, DE 2316706, DE 2316707, DE 2316708, DE 2316709, DE 2316710, DE 2316711, DE 2316712, DE 2316713, DE 2316714, DE 2316715, DE 2316716, DE 2316717, DE 2316718, DE 2316719, DE 2316720, DE 2316721, DE 2316722, DE 2316723, DE 2316724, DE 2316725, DE 2316726, DE 2316727, DE 2316728, DE 2316729, DE 2316730, DE 2316731, DE 2316732, DE 2316733, DE 2316734, DE 2316735, DE 2316736, DE 2316737, DE 2316738, DE 2316739, DE 2316740, DE 2316741, DE 2316742, DE 2316743, DE 2316744, DE 2316745, DE 2316746, DE 2316747, DE 2316748, DE 2316749, DE 2316750, DE 2316751, DE 2316752, DE 2316753, DE 2316754, DE 2316755, DE 2316756, DE 2316757, DE 2316758, DE 2316759, DE 2316760, DE 2316761, DE 2316762, DE 2316763, DE 2316764, DE 2316765, DE 2316766, DE 2316767, DE 2316768, DE 2316769, DE 2316770, DE 2316771, DE 2316772, DE 2316773, DE 2316774, DE 2316775, DE 2316776, DE 2316777, DE 2316778, DE 2316779, DE 2316780, DE 2316781, DE 2316782, DE 2316783, DE 2316784, DE 2316785, DE 2316786, DE 2316787, DE 2316788, DE 2316789, DE 2316790, DE 2316791, DE 2316792, DE 2316793, DE 2316794, DE 2316795, DE 2316796, DE 2316797, DE 2316798, DE 2316799, DE 2316800, DE 2316801, DE 2316802, DE 2316803, DE 2316804, DE 2316805, DE 2316806, DE 2316807, DE 2316808, DE 2316809, DE 2316810, DE 2316811, DE 2316812, DE 2316813, DE 2316814, DE 2316815, DE 2316816, DE 2316817, DE 2316818, DE 2316819, DE 2316820, DE 2316821, DE 2316822, DE 2316823, DE 2316824, DE 2316825, DE 2316826, DE 2316827, DE 2316828, DE 2316829, DE 2316830, DE 2316831, DE 2316832, DE 2316833, DE 2316834, DE 2316835, DE 2316836, DE 2316837, DE 2316838, DE 2316839, DE 2316840, DE 2316841, DE 2316842, DE 2316843, DE 2316844, DE 2316845, DE 2316846, DE 2316847, DE 2316848, DE 2316849, DE 2316850, DE 2316851, DE 2316852, DE 2316853, DE 2316854, DE 2316855, DE 2316856, DE 2316857, DE 2316858, DE 2316

3900233, EP 0103497, EP 0139464, EP 0158380, EP 0163965, EP 0335386, EP 0435811, EP 0449216, EP 0459505, EP 0470805, EP 0490823, EP 0506194, EP 0553174, EP 0557016, EP 0626939, EP 0664289, EP 0671389, EP 0685474, EP 0736532, EP 0738715, EP 0748805, EP 0763534, EP 0816357, EP 0819688, EP 0848000, JP 92234389, JP 94329652, JP 95010875, JP 98072415, JP 98147585, 5,739,144, WO 9117991, WO 9200968, WO 9212961, WO 9307146, WO 931504, 9319068, WO 9319720, WO 9319747, WO 9319749, WO 9319751, WO 9325517, 9420455, WO 9422852, WO 9427947, WO 9500516, WO 9501338, WO 9501980, 9504046, WO 9505386, WO 9508534, WO 9509623, WO 9509624, WO 9509627, 9514680, WO 9514681, WO 9517392, WO 9517399, WO 9519362, WO 9520578, 9527692, WO 9535281, WO 9535283, WO 9535284, WO 9600218, WO 9601825, 9611690, WO 9611917, WO 9612720, WO 9631486, WO 9631487, WO 9635683, 9636611, WO 9636625, WO 9636626, WO 9636638, WO 9638150, WO 9639408, 9704779, WO 9705105, WO 9708143, WO 9709345, WO 9712895, WO 9718208, 9722585, WO 9722586, WO 9723457, WO 9723460, WO 9723461, WO 9724117, 9728131, WO 9730999, WO 9731000, WO 9732853, WO 9735854, WO 9736905, 9744036, WO 9744322, WO 9747604, WO 9748697, WO 9804534, WO 9805327, 9807715, WO 9808828, WO 9808830, WO 9808841, WO 9808844, WO 9809946, 9814448, WO 9818796, WO 9821207, WO 9821208, WO 9821209, WO 9822453, 9845268, WO 9855481, WO 9856756, WO 9905111, WO 9905112, WO 9505113, 9931071, WO 9931090, WO 9947505, WO 9957115, WO 9957118, WO 9964414, 0042017, WO 0042018, WO 0042019, WO 0042020, WO 0042034, WO 0119818, 0151470, WO 0206239, WO 0206270, WO 0205616 and WO 0206238.

[0014] In addition, PDE4 and PDE3/4 inhibitors are exemplary exhibited on the following formulae:

[0015] In the above cited formulae there is given neither any stereochemical information indicated [--O is accordingly --OH, --N is NH, --N is NH.sub.2. Methyl groups, e.g. by lines].

[0016] Furthermore, those PDE4 inhibitors and PDE3/4 inhibitors are preferred where example and/or claimed generically in the patent applications or patents EP 0163 0435811, EP 0482302, EP 0499216, EP 0506194, EP 0510562, EP 0528922, EP 0 WO 9500516, WO 9501338, WO 9600218, WO 9603399, WO 9611690, WO 9636 9728131, WO 9735854, WO 9740032, WO 9743288, WO 9809946, WO 9807715, 9821208, WO 9821209, WO 9822453, WO 9831674, WO 9840382, WO 9855481, 9905113, WO 9931071, WO 9931090, WO 9947505, WO 9957115, WO 9957118, 0012501, WO 0042017, WO 0042018, WO 0042019, WO 0042020, WO 0042034, 0130777, WO0151470, WO 0206239, WO 0206270, WO 0205616 and WO 02062 following research codes: CDC-998, D-4396, SCH-351591, IC-485, CC-1088 and oral availability are preferred here.

[0017] More particularly preferred PDE4 inhibitors or PDE3/4 inhibitors are the compounds CDC-998, SH-636, D-4396, SCH-351591, IC-485, CC-1088, KW-4490 and 3-[3-(4-ethylamino)-8-isopropyl-3H-purin-6-yl]-N-[9-methyl-1,2,3,4-tetrahydropyrrolo[3,2,1-jk][1,4]benzo-diazepin-3(R)-yl]pyridine-4-carboxamide [Research-Code: V-11294A], N-[3-(4-dimethoxyphenyl)thiazole-2-carboxamideoxime [Research-Code: ORG-20241], 3-propyl-1H-purine-2,6-dione [INN: AROFYLLINE], 3-[3-(Cyclopentylloxy)-4-methoxyphenyl]-N-(1-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydro-6H-benzo-[c][1,6]naphthylidene [INN: PUMAFENTRINE], N-(3,5-dichloro-4-pyridinyl)-1H-indol-3-yl]-2-oxoacetamide [Research-Code: AWD-12-281], N-(3,5-dichloro-4-fluorobenzyl)-1H-indol-3-yl]-2-oxoacetamide [Research-Code: AWD-12-343], 8-xanthine [INN: CIPAMFYLLINE], Tetrahydro-5-[4-methoxy-3-[(1S,2S,4R)-2-norbornyl]-1,3-dihydropropanamide [Research-Code: CDC-801], Methanesulfonic acid 2-(2,4-dichlorophenyl) ester [Research-Code: BAY-19-8004], (Z)-5-(3,5-dimethyl-4-hydroxybenzyl) [INN: DARBUFELONE], cis-[4-Cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexyl] [INN: CILOMILAST] and 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyridin-4-yl) [INN: ROFLUMILAST].

[0018] Most particularly preferred PDE4 inhibitors or PDE3/4 inhibitors are 3-Cyclopropyl-N-(3,5-dichloropyridin-4-yl)-benzamide [INN: ROFLUMILAST] and (-)-cis-9-ethoxy-6-(4-diisopropylaminocarbonylphenyl)-benzo-[c][1,6]naphthylidene [INN: D-4396] inhibitor N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide N-oxide is described in WO95/01338.

[0019] In a further embodiment of this invention, there is provided the use of (-)-1,2,3,4,4a, 10b-hexahydro-6-(4-diisopropylaminocarbonylphenyl)-benzo-[c][1,6]PUMAFENTRINE] or a pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the treatment of cachexia.

[0020] In a further embodiment of this invention, there is provided the use of 3-(difluoromethoxy-N-(3,5-dichloropyrid-4-yl))-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the treatment of cachexia.

[0021] In the context of the present invention, unless otherwise stated, a pharmaceutically active ingredient means a pharmaceutically acceptable salt or solvate (e.g. hydrate or solvate of such salt, a pharmaceutically acceptable N-oxide or a pharmaceutically acceptable derivative thereof).

[0022] According to this invention, suitable pharmaceutically acceptable salts refer to acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid in salt preparation depending on whether it is a mono- or polybasic acid and depending on the equimolar quantitative ratio or one differing therefrom. Furthermore, the active ingredient may be present as pure enantiomers or as enantiomer mixtures in any mixing ratio.

[0023] In addition, suitable pharmaceutically acceptable salts also refer to salts with sodium, potassium) or calcium, aluminium, magnesium, titanium, ammonium, and also employ bases in salt preparations in an equimolar quantitative ratio or deviating therefrom.

[0024] PDE4 inhibitors and PDE3/4 inhibitors used in the present invention are in all stereoisomeric forms. The invention encompasses all stereoisomers of PDE4 inhibitors and PDE3/4 inhibitors, including racemates. Tautomers of PDE4 inhibitors and PDE3/4 inhibitors and mixtures thereof are also part of the present invention.

[0025] In a further embodiment of this invention, there is provided the use of 3-(difluoromethoxy-N-(3,5-dichloropyrid-4-yl))-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable solvate (e.g. hydrate) thereof, or a pharmaceutically acceptable salt or solvate of the latter for the manufacture of a pharmaceutical composition for the treatment of cachexia.

[0026] According to this invention, treatment refers to the administration of a pharmaceutically acceptable derivative thereof in a human, whereby the activity of the inhibitor or pharmaceutically acceptable derivative thereof results in suppression of the induction of cachectic symptoms or in influencing the bioactivity of several cytokines. Treatment also refers to prophylaxis which itself refers to measures designed to prevent the dissemination of cachexia.

[0027] In a further embodiment of this invention, there is provided the use of a pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the treatment of cachexia as a result of cancer, chronic cardiac insufficiency, cirrhosis of the liver and chronic infections, burns, COPD, chronic kidney insufficiency, malaria, hypoparathyroidism or Addison's disease.

[0028] In particular, the use of a PDE4 inhibitor or a PDE3/4 inhibitor or a pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the treatment of cachexia is preferred.

[0029] According to this invention, cancer refers to a cancer selected from the group consisting of: ovarian cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, colorectal cancer, thyroid cancer, pancreatic cancer, prostate cancer and bladder cancer.

[0030] In a further embodiment of this invention, there is provided the use of a pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the suppression of cytokines involved in the induction of a cachectic symptom.

[0031] According to this invention, suppression of cytokines refers to decreasing the level of cytokines (i.e. TNF- $\alpha$ , IL-1, IL-6, IFN- $\gamma$ , LIF or CNTF) in patients suffering from cachexia.

concentration of said cytokines measurable in healthy humans.

[0032] In accordance with this invention, a cachectic symptom refers to a symptom of weight loss, anorexia, loss of protein mass, loss of fat mass, muscle atrophy or water.

[0033] In accordance with this invention, PDE4 inhibitors or PDE3/4 inhibitors or derivatives thereof are used for the preparation of a pharmaceutical composition. may be part of a pharmaceutical composition, a pharmaceutical product or a preparation admixture with one or more pharmaceutically acceptable auxiliaries and/or excipients

[0034] The person skilled in the art is familiar with pharmaceutical compositions, preparations and therefore, on the basis of his/her expert knowledge, the person excipients or auxiliaries are suitable for the desired pharmaceutical composition, preparation. In addition to solvents, gel-forming agents, tablet excipients and other person skilled in the art knows to use, for example, antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants or permeation promoters and other

[0035] According to the present invention, a pharmaceutical composition comprising inhibitor for the treatment of cachexia is administered orally, parenterally, intravenously, particular, oral administration and intravenous administration are preferred.

[0036] In case of a pharmaceutical composition (the term "pharmaceutical composition" or "pharmaceutical preparation"), which is intended for oral administration, the therapeutic medicament according to processes known per se and familiar to the person skilled in the art employed as medicament, preferably in combination with suitable pharmaceutical excipients, coated tablets, capsules, emulsions, suspensions or solutions, whereby the PDE4 advantageously is between 0.1 and 95%, preferably between 1 and 80%, particularly By appropriate choice of the excipients and the auxiliaries it is possible to achieve precisely tailored to the active ingredient(s) and/or to the desired onset of action (enteric form).

[0037] Injectable preparations, for example, sterile injectable aqueous or oleaginous formulated according to the known art using suitable dispersing or wetting agents. injectable preparation can also be a sterile injectable solution or suspension in a suitable solvent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles employed are water, Ringer's solution, and isotonic sodium chloride solution. In a conventionally employed as a solvent or suspending medium. For this purpose an including synthetic mono- or diglycerides. Furthermore, fatty acids, such as oleic acid, injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents

[0038] In general, satisfactory results will be obtained when the total daily dosage of inhibitors, when taken orally or intravenously is in the range from 1-2000 µg/kg of body weight, particularly preferred PDE4 inhibitor ROFLUMILAST, the daily dosage is in a range from 1-2000 µg/kg of body weight. The daily dosage for the particularly preferred PDE3/4 inhibitor PUMAFENTRINE is in the range from 1-2000 µg/kg of body weight.

[0039] In case of oral administration of 3-cyclopropylmethoxy-4-difluoromethoxybenzamide (ROFLUMILAST), the adult daily dose is in the range from 50-1000 µg, preferably 500 µg, preferably by once daily administration.

[0040] In case of intravenous administration of 3-cyclopropylmethoxy-4-difluoromethoxybenzamide (ROFLUMILAST), the adult daily dose is in the range from 50-600 µg, preferably 300 µg.

[0041] In a further embodiment of this invention, there is provided the use of a pharmaceutical composition comprising a pharmaceutically acceptable derivative thereof for the manufacture of a pharmaceutical composition for the survival period of a cancer patient afflicted to cachexia.

[0042] In a further embodiment of this invention, there is provided a method for the treatment of cachexia characterized by administration of a pharmaceutical composition comprising a PDE4 inhibitor or a pharmaceutically acceptable derivative thereof.

[0043] In a further embodiment of this invention, there is provided a method for the treatment of cachexia characterized by administration of a pharmaceutical composition comprising a PDE4 pharmaceutically acceptable derivative thereof, whereby cachexia is a result of cachexia

acute and chronic infections, burns, chronic cardiac insufficiency, cirrhosis of the liver, renal insufficiency.

[0044] In a further embodiment of this invention, there is provided a method for characterized by administration of a pharmaceutical composition comprising a PD pharmaceutically acceptable derivative thereof, whereby the PDE4 inhibitor or the pharmaceutically acceptable derivative thereof is effective to suppress cytokines in symptom.

[0045] In a further embodiment of this invention, there is provided a method for afflicted to cancer comprising the step of administering an effective amount of a f a pharmaceutically acceptable derivative thereof.

[0046] In a further embodiment of this invention, there is provided a method for afflicted to cancer comprising the step of administering an effective amount of a pharmaceutical derivative thereof, whereby the survival period of a patient is enlarged.

[0047] In a further embodiment of this invention, there is provided a method for and/or radiation-therapy in a human afflicted to cancer and cachexia comprising 1 amount of a chemotherapeutic agent and/or radiation and an effective amount of or a pharmaceutically acceptable derivative thereof.

[0048] According to this invention, improving the response to chemo- and/or rad cancer and cachexia refers to prolonging the survival period of said human. In pa interval of time a human afflicted to cancer and cachexia survives after having ch

[0049] According to this invention, a PDE4 inhibitor or a PDE3/4 inhibitor or a pharmaceutical composition thereof may be administered before, during and/or after radiation. It may be also administered before, during and after radiation, during and after, before and after, or before, during and after radiation.

[0050] According to this invention, the source of radiation can be external or internal. Radiation is administered in accordance with known techniques known to a person skilled in the art of radiation therapy or brachytherapy, i.e. a therapy carried out by placing the source of radiation depends on numerous factors as is well known in the art. Such factors include the location of healthy organs in the path of the radiation that might be adversely affected, the type of radiation therapy, and the area of the body in need of treatment. The dose will typically be particular between 2 and 80 Gy.

[0051] According to this invention, chemotherapy refers to treatment with a chemotherapeutic agent. In accordance with this invention, a PDE4 inhibitor or a PDE3/4 inhibitor or a pharmaceutical composition thereof may be administered before, during, after, before and during, during and after, and during and after treatment with a chemotherapeutic agent.

[0052] According to this invention, chemotherapeutic agent is a chemotherapeuti consisting 5 FU, actinomycin D, ABARELIX, ABCIXIMAB, ACLARUBICIN, ADAPALEI AMINOGLUTETHIMIDE, AMIPRILOSE, AMRUBICIN, ANASTROZOLE, ANCITABINE, , BASILIXIMAB, BENDAMUSTINE, BICALUTAMIDE, BLEOMYCIN, BROXURIDINE, BU CARBOPLATIN, CARBOQUONE, CARMUSTINE, CETRORELIX, CHLORAMBUCIL, CHL CLADRIBINE, CLOMIFENE, CYCLOPHOSPHAMIDE, DACARBAZINE, DACLIZUMAB, I DESLORELIN, DEXRAZOXANE, DOCETAXEL, DOXIFLURIDINE, DOXORUBICIN, DR EDELFSOSINE, EFLORNITHINE, EMITEFUR, EPIRUBICIN, EPTIOSTANOL, EPTAPLAT ETOPOSIDE, EXEMESTANE, FADROZOLE, FINASTERIDE, FLOXURIDINE, FLUCYTO FLUTAMIDE, FORMESTANE, FOSCARNET, FOSFESTROL, FOTEMUSTINE, FULVESTI GLIVEC, GOSERELIN, GUSPERIMUS, HERCEPTIN, IDARUBICIN, IDOXURIDINE, IFI INFLIXIMAB, IRINOTECAN, LANREOTIDE, LETROZOLE, LEUPRORELIN, LOBAPLATI MERCAPTOPURINE, METHOTREXATE, METUREDEPA, MIBOPLATIN, MIFEPRISTONE MITOGUAZONE, MITOLACTOL, MITOMYCIN, MITOXANTRONE, MIZORIBINE, MOTE NEBAZUMAB, NEDAPLATIN, NILUTAMIDE, NIMUSTINE, OCTREOTIDE, ORMELOXIF PALIVIZUMAB, PEGASPARGASE, PEGFILGRASTIM, PENTETREOTIDE, PENTOSTATI PIRARUBICIN, PLICAMYCIN, PREDNIMUSTINE, PROCARBAZINE, PROPAGERMANIL RALTITREXED, RANIMUSTINE, RANPIRNASE, RASBURICASE, RAZOXANE, RITUXII ROMURTIDE, RUBOXISTAUIN, SARGRAMOSTIM, SATRAPLATIN, SIROLIMUS, SO STREPTOZOCIN, TAMOXIFEN, TASONERMIN, TEGAFUR, TEMOPORFIN, TEMOZOLC THIOTEPA, THYMALFASIN, TIAMIPRINE, TOPOTECAN, TOREMIFENE, TRASTUZUM. TRIMETREXATE, TRIPTORELIN, TROFOSFAMIDE, UREDEPA, VALRUBICIN, VERTEP



VINDESINE, VINOELBINE and VOROZOLE.

## FIGURES

[0053] FIG. 1: Effects of Zardaverine (left graph) and Piclamilast (right graph) on lung adenocarcinoma Xenograft explants. Tumor fragments from mice carrying L cell suspensions were seeded into 24 Well plates. After seeding of the cells, Zardaverine and 0.1 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.3 and 0.001 .mu.M, respectively, supernatants were harvested 24 hours later. IL-1 content of the supernatants was quantitated using ELISA kits according to the manufacturer's recommendations. Zardaverine (left graph) was able to suppress the secretion of IL-1 from 85.3 pg/ml in control supernatants (treated with the respective amount of DMSO) to 77.1 pg/ml at concentrations of 100, 3, and 0.1 .mu.M, respectively. Piclamilast (right graph) was able to suppress the secretion of IL-1 from 85.3 pg/ml in control supernatants (treated with the respective amount of DMSO) to 64.4, and 81.9 pg/ml at concentrations of 1; 0.3, and 0.001 .mu.M, respectively.

[0054] FIG. 2: Effects of Zardaverine (left graph) and Piclamilast (right graph) on hypernephroma Xenograft explants. Tumor fragments from mice carrying RXF 39 cell suspensions were seeded into 24 Well plates. After seeding of the cells, Zardaverine and 0.1 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.01 and 0.001 .mu.M, respectively, supernatants were harvested 24 hours later. IL-1 content of the supernatants was quantitated using ELISA kits according to the manufacturer's recommendations. Zardaverine (left graph) was able to suppress the secretion of IL-1 from 46.9 pg/ml in control supernatants (treated with the respective amount of DMSO) to 48.1 pg/ml at concentrations of 100 and 0.1 .mu.M, respectively. Piclamilast (right graph) was able to suppress the secretion of IL-1 from 46.9 pg/ml in control supernatants (treated with the respective amount of DMSO) to 43.2 pg/ml at concentrations of 1; 0.01, and 0.001 .mu.M, respectively.

[0055] FIG. 3: Effects of Zardaverine (left graph) and Piclamilast (right graph) on LXFA 526 lung adenocarcinoma Xenograft explants. Tumor fragments from mice were excised and cell suspensions were seeded into 24 Well plates. After seeding of the cells, Zardaverine and 100, 3, and 0.1 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.3 and 0.001 .mu.M, respectively, supernatants were harvested 24 hours later. TNF.alpha. content of the supernatants was quantitated using R&D Quantikine ELISA kits according to the manufacturer's recommendations. Zardaverine (left graph) was able to suppress the secretion of TNF.alpha. from 16.8 pg/ml in control supernatants (treated with the respective amount of DMSO) to 12.6; 12.9, and 13.8 pg/ml at concentrations of 100, 3, and 0.1 .mu.M, respectively. Piclamilast (right graph) was able to suppress the secretion of TNF.alpha. from 16.8 pg/ml in control supernatants (treated with the respective amount of DMSO) to 13.9; 15.1, and 17.2 pg/ml at concentrations of 1; 0.3, and 0.001 .mu.M, respectively.

[0056] FIG. 4: Effects of Zardaverine (left graph) and Piclamilast (right graph) on LXFE 397 epidermoid adenocarcinoma Xenograft explants. Tumor fragments from mice were excised and cell suspensions were seeded into 24 Well plates. After seeding of the cells, Zardaverine and 30, 10, and 3 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.3 and 0.001 .mu.M, respectively, supernatants were harvested 24 hours later. TNF.alpha. content of the supernatants was quantitated using R&D Quantikine ELISA kits according to the manufacturer's recommendations. Zardaverine (left graph) was able to suppress the secretion of TNF.alpha. from 30.3 pg/ml in control supernatants (treated with the respective amount of DMSO) to 20.1; 28.2, and 27.7 pg/ml at concentrations of 100, 3, and 0.1 .mu.M, respectively. Piclamilast (right graph) was able to suppress the secretion of TNF.alpha. from 30.3 pg/ml in control supernatants (treated with the respective amount of DMSO) to 20.1; 28.2, and 27.7 pg/ml at concentrations of 100, 3, and 0.1 .mu.M, respectively.

## EXAMPLE

[0057] Effectiveness of PDE3/4 and PDE4 inhibitors in the suppression of cytokine cachexia.

[0058] The PDE3/4 inhibitors Zardaverine and PDE4 inhibitor Piclamilast were utilized to test the suitability of PDE4 and/or PDE3/4 inhibitors in the suppression of cachexia-induced weight loss.

[0059] To this end primary cultures of tumor cells were derived from cachexia induced mice. The xenograft cell derivatives and their measurable parameters are listed in Table 1. TABLE-US-00001 TABLE 1 TNF.alpha. Tumor Histology IL-1 comment  
PXC adenocarcinoma (lung) + + LXFE397 epidermoid not detectable +

[0060] 5 to 10 NMRI nude mice were implanted with tumor fragments derived from LXFE397 epidermoid adenocarcinoma and grown until the tumors reached approximately 0.5 g, which correlated well with cachexia. Mice were then sacrificed and tumors were excised. Cells were subsequently isolated using mechanical disintegrators, proteases, hyaluronidase, and DNase I. The crude suspension was then used for the measurement of cytokine levels.

sterile sieves with diameters of 200 and 50  $\mu\text{m}$ , respectively.

[0061] Washed cell pellets were resuspended in Iscove's modified Dulbecco's Medium. 0.24 to 1 times  $10^6$  tumor cells were seeded in 24 well plates. The cell isolates also blood cells and stromal elements of murine origin. The cell lines RXF 486L and 1 times  $10^6$  cells were seeded into each well.

[0062] Piclamilast and Zardaverine were dissolved in 100% DMSO (dimethyl sulfoxide) concentration of 1  $\mu\text{M}$  to 0.001  $\mu\text{M}$  (Piclamilast) or 100  $\mu\text{M}$  to 0.1  $\mu\text{M}$  (Zardaverine) and plated at the same time. 24 hours after seeding supernatants were collected, centrifuged, and analyzed.

[0063] For the quantitative measurement of IL-1, IL-6, and TNF- $\alpha$ , respectively, using Quantikine ELISA Kits from R&D Systems according to the manufacturer's instructions.

[0064] Modulation of IL-1 expression was investigated in two cell systems: LXFA and Piclamilast were in both cell lines able to suppress IL-1 levels with Zardaverine. Piclamilast (results are shown in FIGS. 1 and 2).

[0065] The modulation of TNF- $\alpha$  levels by Zardaverine and Piclamilast was investigated in the LXFE 397 model, as shown in FIGS. 3 and 4. In both cell systems, Zardaverine suppressed the secretion of TNF- $\alpha$  by the respective cell isolates into the medium.

[0066] These data show that PDE4 as well as PDE 3/4 inhibitors have the potential to suppress cytokines linked to cachexia from tumor cell isolates that originate from cachexia. It is noted that COX-2 inhibitors that to some extent exert anti-cachectic activity depending on the dose investigated, were unable in this system to suppress the secretion of either IL-1 or TNF- $\alpha$  in the above described system.

**Desktop File Security** - Protect All the Files You Have  
Easy, Fast, Secure & Affordable. [PinionSoftware.com](http://PinionSoftware.com)

**<- Previous Application (Synergistic combination) | Next Application (Preparation of the preparation) ->**

**Patent RSS Feeds**

Copyright © 2003-2007 FreePatentsOnline.com. All rights reserved. **Contact Us.** [info@freepatentsonline.com](mailto:info@freepatentsonline.com)